UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,702	11/21/2003	Tomoyuki Tokunaga	3462.1007-000	1351

21005 7590 03/01/2006

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
PARAS JR, PETER	.

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,702	TOKUNAGA ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/2/06.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-34 is/are pending in the application.

4a) Of the above claim(s) 8-34 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 21 November 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4262004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-34 are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-7, in the reply filed on 2/2/06 is acknowledged.

Claims 8-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/2/06.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of sorting undifferentiated cells, comprising contacting the cells with an antibody to a cell-surface antigen (particularly PECAM-1, SSEA-1, SSEA-3, and SSEA-4), and sorting the undifferentiated cells according to the presence or absence of the binding to the antibody.

The specification has discussed the invention as featuring methods of sorting undifferentiated cells having characteristics such as the potential for efficient chimera formation and the ability to form normal individuals following nuclear transplantation. See page 6, at lines 15-20. The specification has asserted that cells of the invention include embryonic stem (ES) and embryonic germ (EG) cells. The specification has further asserted that detection of antigens such as PECAM-1, SSEA-1, SSEA-3 and SSEA-4 correlated with sorting of undifferentiated cells. The specification has provided guidance correlating to sorting of mouse ES cells that express PECAM-1 and SSEA-1. However, the specification has failed to provide guidance correlating to sorting of undifferentiated cells according to expression of PECAM-1, SSEA-1, SSEA-3 and SSEA-4. It is unpredictable, given variability of expression of PECAM-1, SSEA-1, SSEA-3 and SSEA-4 across species, if undifferentiated cells can be sorted based on expression patterns of PECAM-1, SSEA-1, SSEA-3 and SSEA-4. Given, the lack of guidance provided by the specification it would require undue experimentation for one of skill in the art to practice the invention as claimed without a reasonable expectation of success.

As a first issue, the claims are directed to methods of sorting of undifferentiated cells. The specification has asserted that sorted undifferentiated cells may be used for constructing chimeric embryos, which can be made by either injection of ES cells into a blastocyst or nuclear transfer. See pages 7-8 of the specification. With respect to injection of ES cells into a blastocyst for creating a chimeric embryo, it is well known that such technology is limited to ES cells obtained from mouse. This is because to

date, ES cell technology is limited to the mouse system as only mouse ES cells achieve germline transmission of a genetic modification. See Hochepied et al (Stem Cells, 2004, 22: 441-447) in the abstract, which reports "Transmission of the genotype to the offspring of chimeras has only been achieved with *M. musculus* ES cells; limiting targeted mutagenesis using ES cells to this species". Although transmission of ES-cell derived genome to the germ cells and further to the offspring has proved impossible in species other than the house mouse *M. musculus*, Hochepied et al has further reported that "even within *M. musculus* species certain genetic backgrounds have been reported to be less permissive or even non-permissive for germline –competent ES cell derivation. See the first paragraph, in the second column of page 444. Schoonjans et al (Stem Cells, 2003, 21: 90-97) supports the findings of Hochepied by observing that efficiency of derivation of germline-competent ES cell lines from inbred mouse strains, with specific genetic backgrounds, is greatly strain dependent. See page 90 of Schoonjans, in the introduction. Given the state of the art it would appear that germline contribution of ES cells is undeveloped and unpredictable in species other than mouse as well as within the various strains of inbred mice. Therefore, it is unpredictable if undifferentiated cells (ES cells), which contribute to germline, could be isolated from species other than mouse. Accordingly, given the undeveloped state of the art with respect to availability of ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and use the invention as claimed without a reasonable expectation of success.

As a final issue, the claims correlate the presence or absence of cell-surface antigens, particularly PECAM-1, SSEA-1, SSEA-3 and SSEA-4, with sorting of undifferentiated cells. The specification has asserted that expression of cell-surface markers such as PECAM-1, SSEA-1, SSEA-3 and SSEA-4 could correlate to undifferentiated cells. However, given the state of the art, it is unpredictable if expression of cell-surface markers such as PECAM-1, SSEA-1, SSEA-3 and SSEA-4 actually correlated with undifferentiated cells. First, ES cells from all species do not express the same surface markers. The specification, at pages 6-7, observed that mouse and human ES cells do not express the same markers. For example, the specification reported that mouse ES cells express PECAM-1 and SSEA-1 while human ES cells express SSEA-3 and SSEA-4. The art supports the observations reported by the specification with respect to species-specific differences in expression of SSEA-1, SSEA-3 and SSEA-4. See US 5,843,780 at columns 9-10, as well as in Table 1 at column 11. Moreover, even within subpopulation of mouse ES cells variability exists with respect to marker expression. See Cui et al (Journal of Histochemistry, 2004, 52(11): 1447-1457). Cui et al reported that within mouse ES cells, heterogeneity was evident for PECAM-1 and SSEA-1 distribution; subpopulations of ES cells expressed either PECAM-1 alone, SSEA1 alone or both. Although the reasons for heterogeneity are not clear, Cui et al theorized that cells with different differentiation fates might be randomly distributed in ES cell colonies as they are in mouse embryos. See page 1452. Furthermore, it is unpredictable if expression of markers such as PECAM-1, SSEA-1, SSEA-3 and SSEA-4 is limited to undifferentiated cells. The state of the art has set

forth that expression of PECAM-1, SSEA-1, SSEA-3 and SSEA-4 is not limited to undifferentiated cells. For example, Kannagi et al (EMBO, 1983, 2(12): 2355-2361) reported SSEA-3 and SSEA-4 are expressed on the surface of human teratocarcinoma cells. See page 2355. Teratocarcinoma cells do not share the same potency as ES cells and are unable to contribute to the germline. Teratocarcinoma cells are considered to be in a differentiation state different from that of ES cells given their inability to contribute to the germline and limited potency. Moreover, Kannagi et al further observed that SSEA-1 is expressed during differentiation of human teratocarcinoma cells. See the abstract and throughout the entire document. Finally Kannagi et al reported that SSEA-4 is expressed on human erythrocytes, which are differentiated cells. The observations of Kannagi et al suggested that expression of SSEA-1, SSEA-3 and SSEA-4 is associated with differentiated cells. In addition, Cui et al discussed that expression of PECAM-1 is not limited to undifferentiated cells. In fact, it is well known in the art that PECAM-1 is expressed not only in differentiated ES cells but also in differentiated cells such as endothelial cells and leukocytes. Collectively, the teachings of Kannagi et al and Cui et al suggested that expression of markers such as PECAM-1, SSEA-1, SSEA-3 and SSEA-4 is not limited to undifferentiated cells. Therefore, given the teachings of the prior art it is unpredictable if undifferentiated cells can be sorted based on expression of PECAM-1, SSEA-1, SSEA-3 and SSEA-4. Given, the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to practice the methods as claimed without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the sorting of undifferentiated cells, the lack of direction or guidance provided by the specification correlating to sorting of undifferentiated cells, the absence of working examples for the demonstration or correlation to the sorting of undifferentiated cells, the unpredictable state of the art with respect to expression of cell-surface markers as indicators of undifferentiated cells, the undeveloped state of the art pertaining to use of ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson J (US 5,843,780).

The claims are directed to methods of sorting undifferentiated cells, particularly embryonic stem or germ cells, wherein the sorting is based on the presence or absence of the binding of an antibody to an antigen, particularly PECAM-1, SSEA-1, SSEA-3, and SSEA-4.

Thomson taught methods of isolating (sorting) primate ES cells based on the presence of cell-surface markers, SSEA-3 and SSEA-4, and the absence of cell-surface marker, SSEA-1. The presence or absence of the cell-surface markers was determined by binding of an antibody. See columns 9-11.

Thus, the teachings of Thomson anticipated all of the instant claim limitations.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER